REMARKS

Claims 11, 12, and 15 have been amended and new claims 19-24 have been added. Claims 11-24 are currently pending in the application. All pending claims are set forth in Exhibit A with amendments shown (if applicable).

Applicants gratefully acknowledge the 14 February 2003 interview with the Examiner in which all pending rejections in the application were discussed. In particular, the difference between the polymeric moieties of Grossman (cited below) and the non-oligomeric moieties of Applicants' invention were discussed, and role of the capture ligand in Applicants' invention was explained and differentiated from the use of capture ligands in Babon (cited below).

The specification has been amended to add a paragraph from parent application 09/698,846 that was incorporated by reference into the present application (see page 1, lines 5-8). This paragraph is found on page 9, line 25, to page 10, line 4, of 09/698,846, and has been expressly incorporated by the above amendment because in contains terms used in the claims as noted in the table below.

The specification has also been amended to added a Sequence Listing section to list the sequences set forth on page 49, lines 20-25, and page 60, line 35 of the specification.

Bases for amendments to the claims are as follows:

Claim(s)	Term/Phrase	Basis
11, 19	"a capture agent" as a component of the kit.	Page 4, line 12.
11, 12, 19	"M is a non-oligomeric compound"	Page 30, lines 30-31. Claims 8, 13, and 23 of parent application 09/602,586 that has been incorporated by reference.
11, 19	"released from an electrophoretic probe of the set upon digestion of the electrophoretic probe by a nuclease" in reference to the eTag reporter (D,M)-N.	Page 4, lines 20-28 (describes concept of (D,M)-N being release from electrophoretic probe). Page 31, lines 2-6 (states that the methodology of the invention may be implemented with the nucleases used in polymerase chain reaction and Invader technologies. Page 33, Table 3 (rightmost column entitle "e-tag Release" at top lists four (4) exemplary nucleases for releasing eTag reporters)
11, 19	"in an electropherogram" in reference to distinct peaks of eTag reporters separated by electrophoresis.	Page 5, lines 36-38 (figure caption for Fig. 8) Figure 8.
11, 19	"capture ligand specifically binds to a capture agent to exclude undigested electrophoretic probes from the electropherogram"	Page 4, lines 41-43 and Claim 10 (concept of capture ligand specifically binding to capture agent). Page 4, lines 29-32, and page 24, 14-32

		(describes the function of a capture ligand). Page 6, lines 41-45, Figure captions for Figs. 26 and 27. Figures 26 and 27 showing data wherein undigested probes are excluded from electropherogram using avidin as capture agent. Figure 3B showing diagrammatically the exclusion of undigested probe using capture agent.
19	"molecular weight of between 35 and 1500 daltons" in reference to M.	Page 9, lines 27-31, of parent application 09/698,846*.
17, 22	"capture agent is avidin or streptavidin"	Claim 6.
15, 23	"a nuclease"	Page 4, line 12.
24	Chemical formula for eTag reporters.	Figure 15.

* Parent application 09/698,846 was incorporated by reference (see page 1, lines 5-8, of the specification), and the indicated passage has been expressly incorporated by the above amendment to the specification.

No new matter has been added by the amendments. Reconsideration is respectfully requested.

Rejections Under 35 U.S.C. 103

The Examiner rejected claims 11-14 and 16-18 under 35 U.S.C. 103(a) as being unpatentable over Grossman (5,470,705) in view of Babon (5,851,770). The Examiner argues as follows: Grossman discloses a method and compositions for detecting a plurality of polynucleotide sequences, the compositions comprising a plurality of probes each consisting of an oligonucleotide and a polymer chain that gives the probe a distinct electrophoretic mobility. Babon discloses use of a capture ligand, such as biotin, to capture on a solid phase support various hetero- and homoduplexes that may or may not contain mismatched basepairs. Captured duplexes are treated with a mismatch-recognizing nuclease that cleaves the captured sequences at mismatch locations to release fragments which are then analyzed by electrophoresis. The Examiner argues that it would be obvious to one of ordinary skill to modify the probes of Grossman to include the capture ligands of Babon, thereby obtaining Applicants' invention. One of ordinary skill would be motivated to make such a combination because of the advantages of being able to wash away unbound probe in the solid phase system disclosed by Babon.

Applicants respectfully disagree, particularly in view of the amendments. First, the probes of Grossman differ from those of Applicants' invention in two important aspects: (i) Grossman does not disclose capture moieties attached to probes, as pointed out by the Examiner, and (ii) Grossman discloses only oligonucleotide probes derivatized with *polymer chains* to generate distinct electrophoretic mobilities, whereas Applicants' invention employs probes with *non-*

oligomeric moieties to generate distinct electrophoretic mobilities. The latter difference is important because the non-oligomeric moieties are small molecules, as pointed out on page 14, line 34, of the specification. The small molecular size of the eTag reporter results in faster separations and reduced likelihood of interference with enzymatic cleavage of the eTag reporter from the oligonucleotide probe.

Second, as argued in the prior Amendment, the capture ligand disclosed by Babon (like Grossman) is attached to a target sequence, not a probe, and it is the target sequence that is cleaved in Babon, not a probe. This is in contrast to Applicants' invention where the capture ligand is attached to probes, and the probes are cleaved to release eTag reporters.

Third, Grossman and Babon neither disclose nor suggest the desirability of placing a capture ligand on the probe, as described by Applicants. In this regard, Applicants direct the Examiner to page 24, line 5, to page 25, line 36, of the specification and Figs. 26 and 27 of the application which show the dramatic improvement in signal that occurs by use of capture ligands on probes. As explained in the above passage, capture ligands, such as biotin, are used with a capture agent, such as avidin, to exclude interfering material from the electropherograms, with the dramatic result exemplified by Figs. 26 and 27. The capture ligands of Applicants' are NOT used in a wash step, as disclosed in Babon or in Murtagh, Jr. et al (U.S. patent 5,744,306, see Fig. 16 and col. 31, lines 58-62), but rather are used to impart a mass and charge on uncleaved or partially cleaved probes that excludes them from the electropherogram of the cleaved eTag reporters (see the section of the application entitled, "C. Capture Ligands," cited above).

There is no equivalent observation to those of Figs. 26 and 27, or other suggestion, in either Grossman or Babon or Murtagh that would motivate one of ordinary skill to place the capture ligand of Babon or Murtagh on the probes of Grossman. Applicant submit that the combination of Grossman and Babon would not lead one of ordinary skill to Applicants' invention without an independent inventive contribution, and accordingly respectfully request that the rejection be withdrawn.

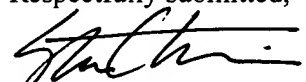
The Examiner rejected claim 15 under 35 U.S.C. 103(a) as being unpatentable over Grossman (cited above) in view of Babon (5,851,770) as applied above, and further in view of Shipman et al (6,403,303). The Examiner applies Grossman and Babon as above and cites Shipman for the disclosure of cleavase in a assay to detect polynucleotide targets. The Examiner argues that it would have been obvious to one of ordinary skill in the art to substitute the polymerase of Grossman with the cleavase of Shipman.

Applicants respectfully disagree. Grossman in view of Babon does not render Applicants' invention obvious for the reasons stated above. Therefore, the mere disclosure that a cleavase, or other nuclease (as the claim 15 presently reads), can be substituted for the polymerase of Grossman to release a reporter molecule still does not overcome the deficiencies of the latter two references. Accordingly, Applicants respectfully request that the rejection be withdrawn.

In view of the above, Applicants submit that the claims as written fully satisfy the requirements of Title 35 of the U.S. Code, and respectfully request that the rejections thereunder be withdrawn and that the claims be allowed and the application quickly passed to issue.

If any additional time extensions are required, such time extensions are hereby requested. If any additional fees not submitted with this response are required, please take such fees from deposit account **50-2266**.

Respectfully submitted,



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Enclosures:

Petition for Time Extension
Declaration of Sequence Listing with 3.5 inch diskette containing
CRF of Sequence Listing

Exhibit A
Paragraphs Added or Modified in the Specification
Showing Amendments (if applicable)

Page 12, after line 41, please insert the following paragraph from parent application 09/698,846:

-- The eTag reporters will vary depending upon the method of detection. Groups of at least 10 eTag reporters bound to 10 different binding compounds will be used in the determinations. The eTag reporters will be characterized by being cleavable from the binding compound in the same vessel by the same cleavage mechanism, having a shared characteristic that permits separation and individual detection, being compatible with the determination method and being in the molecular weight range of about 30 to 3000 dal, usually in the molecular weight range of about 35 to 1500 dal. The variation may be mass using a mass spectrometer, where a magnetic field is used for separation, mass/charge ratio using electrokinesis, where an electric field is used for separation, which may also include sieving and/or adsorbing polymers, adsorption, using chromatography, e.g gas chromatography, high pressure liquid chromatography, where polar and van der Waal interactions are used for separation, etc.--

After page 67, please add the following Sequence Listing:

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-- Sequence Listing

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      MATRAY, Tracy
      CHENNA, Ahmed
<120> Kits employing oligonucleotide-binding e-tag probes
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Currently Pending Claims Showing Amendments (if applicable)

11. (Amended) A kit for detecting the presence or absence of one or more of a plurality nucleotide sequences in a sample, the kit comprising:

a capture agent; and

a plurality of electrophoretic probes selected from the group defined by the formula:

(D, M)-N-T

wherein:

(D, M)-N is an e-tag reporter released from an electrophoretic probe upon digestion of the electrophoretic probe by a nuclease;

D is a detection group;

M is a non-oligomeric compound [~~mobility modifier~~] consisting of from 1 to 500 atoms selected from the group consisting of carbon, hydrogen, oxygen, phosphorus, nitrogen, sulfur, and boron;

N is a nucleotide; and

T is an oligonucleotide specific for at least one of the plurality of nucleotide sequences, each T having a length in the range of from 12 to 60 nucleotides such that at least one nucleotide of T has a capture ligand attached;

and wherein each e-tag reporter of the plurality of electrophoretic probes has a distinct charge/mass ratio so that the e-tag reporters form distinct peaks in an electropherogram upon electrophoretic separation;

and wherein the capture ligand specifically binds to the capture agent to exclude undigested electrophoretic probes from the electropherogram.

12. (Amended) The kit of claim 11 wherein said formula is D-M-N-T and wherein M is a non-oligomeric compound [~~mobility modifier~~] consisting of from 1 to 300 atoms selected from the group consisting of carbon, hydrogen, oxygen, phosphorus, nitrogen, sulfur, and boron.

13. The kit of claim 12 wherein D is a fluorophore, chromophore, or an electrochemical label.

14. The kit of claim 13 wherein said plurality is in the range of from 5 to 100.

15. (Amended) The kit of claim 14 further including a nuclease [~~cleavase~~].

16. The kit of claim 14 wherein said fluorescent label is a fluorescein.

17. (Amended) The kit of claim 14 wherein said capture ligand is biotin wherein said capture agent is avidin or streptavidin.

18. (Amended) The kit of claim 14 further including [~~a~~] said capture agent attached to a solid support.

19. (New) A kit for detecting the presence or absence of one or more of a plurality nucleotide sequences in a sample, the kit comprising:

a capture agent; and

a plurality of electrophoretic probes selected from the group defined by the formula:

(D, M)-N-T

wherein:

(D, M)-N is an e-tag reporter released from an electrophoretic probe of the set upon digestion of the electrophoretic probe by a nuclease;

D is a detection moiety;

M is a non-oligomeric compound having a molecular weight of between 35 and 1500 daltons;

N is a nucleotide; and

T is an oligonucleotide specific for at least one of the plurality of nucleotide sequences, each T having a length in the range of from 12 to 60 nucleotides such that at least one nucleotide of T has a capture ligand attached;

and wherein each e-tag reporter of the plurality of electrophoretic probes has a distinct charge/mass ratio so that e-tag reporters of different electrophoretic probes form distinct peaks in an electropherogram upon electrophoretic separation;

and wherein the capture ligand specifically binds to the capture agent to exclude undigested electrophoretic probes from the electropherogram.

20. (New) The kit of claim 19 wherein D is a fluorophore, chromophore, or an electrochemical label.

21. (New) The kit according to claim 20 wherein said formula is D-M-N-T and wherein said plurality is in the range of from 5 to 100.

22. (New) The kit of claim 21 wherein said capture ligand is biotin and wherein said capture agent is avidin or streptavidin.

23. (New) The kit of claim 21 further including a nuclease.

24. (New) The kit of claim 21 wherein said e-tag reporter is selected from the group consisting of the following compounds: